

REMARKS

This responds to the Office Action mailed on July 25, 2007.

No claims are amended, no claims are canceled, and no claims are added; as a result, claims 113, 119-121, 124, 126, 134-135, 137-138, and 140 are now pending in this application.

Interview Summary

A personal Applicant-initiated Examiner Interview in the above-referenced matter, concerning the Final Office Action dated 07/25/2007, took place at the U.S. Patent Office on Nov. 13, 2007. In attendance were Examiners Christopher M. Gross, Mark Shibuya, and Jon Epperson, and applicants' representative Mark Blaskovich of Mimetica Ltd. (patent licensee) and patent attorneys Gary Speier and Geoffrey Cooper, representing the Applicants.

All presently pending claims not withdrawn, i.e., claims 113, 119-121, 124, 126, 134, 135, 137, 138, and 140 were discussed in view of the claim rejections under 35 USC §102(b) over Ma, and under 35 USC §103 over Gardner in view of Alkorta. The instant pending claims are directed to seven-membered ring structures designed to mimic a particular type of turn in a peptide chain, thus mimicking a domain of a protein made up of a folded peptide chain incorporating this kind of turn. The seven-membered ring structures of the pending claims, termed 1,4-diazepanes, must effectively mimic this turn structure in order to have the desired bioactivity as a medicinal compound. Structures involving other ring sizes are not within the scope of the pending claims.

Concerning the §102 rejection, an exhibit, a Declaration by the inventor herein, Dr. Cassidy, was provided to the Examiners, pertinent to the Applicants' assertion that the Ma reference cannot be used as the basis for a §102 rejection because Ma is not enabling to a person of ordinary skill. The Declaration presented evidence in support of the Applicants' assertion that Ma had actually prepared an isomer of the structure shown in the Ma reference, not the seven-membered ring product shown therein that Ma believed he had obtained. The structure shown by Ma had been used by the Examiner as the basis for the §102 rejection. The report described results of experiments that had been carried out, duplicating Ma's experimental procedures, and providing spectroscopic data in support of the assertion that Ma's product was not in fact a

seven-membered ring such as are claimed in the instant application, but was an isomeric three- or five-membered ring structure that was misidentified by Ma.

Arguments were then presented to the Examiners in attendance. With respect to the §102 rejection, applicants first addressed the Examiner's assertion that Ma disclosed two separate routes to his alleged seven-membered ring product. It is Applicants' position that Ma only disclosed two separate possible routes to the single precursor compound for the cyclization reaction alleged to produce the seven-membered ring compound, not to the seven-membered ring compound itself. The Examiner apparently found this argument unpersuasive, but could not direct applicants' attention to any language in support of there being a second route used in a final step in the direct preparation of the seven-membered ring product. The sole process that Applicants believe to be disclosed by Ma, alleged to yield the seven-membered ring product, a Mitsunobu reaction, was duplicated as described in the Declaration exhibit. It is the Applicants' position that there is no second approach was disclosed by Ma to be duplicated.

Then, Applicants discussed the spectroscopic evidence provided in the Declaration in support of the alternative isomeric structure that Ma had in fact obtained, as opposed to the seven-membered ring structure that Ma thought he had obtained. The Examiner seemed to feel that even if the major product isolated from the reactions carried out by Dr. Cassidy and presented in the declaration was not Ma's structure, insufficient investigation had been conducted to have a high degree of certainty that the seven-membered ring compound was not also present in the reaction product in some yield, that would serve to provide enablement to the person of ordinary skill using Ma's method. The Applicants also understood the Examiner to assert that Ma's disclosed structure and synthetic approach, coupled with a reasonable degree of experimentation in variation of reaction condition such as a person of ordinary skill could be expected to carry out, could in fact make Ma enabling, and thus anticipatory. Alternatively, it is believed that the Examiner took the position that Ma's structural disclosure, combined with the knowledge of a person of ordinary skill, would make the instant pending claims obvious over Ma. Applicants maintained that if the Mitsunobu cyclization reaction failed to take place in the manner disclosed by Ma, as Applicants' data suggests, that it is not within ordinary skill to prepare the difficult seven-membered ring structure without undue experimentation. Furthermore, having found that Ma's Mitsunobu conditions failed, Applicants believe that a

person of ordinary skill would be motivated against extensive exploration of Mitsunobu conditions, and that no generally known alternative reactions using those precursors are available.

The Applicants then attempted to determine what nature and quantity of evidence would be required for the Examiner to find sufficiently persuasive to overcome the presumption of validity of the Ma reference. The Examiner indicated, as Applicants understand it, that he thought a factorial series of reactions should be run, exploring to a reasonable extent (without undue experimentation) variations in reaction conditions. Furthermore, each reaction product should be carefully analyzed for trace amounts of the seven-membered ring product, down to about the 1% yield level, as the seven-membered ring compound would have to be recoverable from the reaction for the process to be enabled and yields of less than about 1% would be impractical in that regard.

As discussed below, Applicants have now carried out just such a series of experiments, the results of which are presented in the new Declaration submitted herewith. The results of the experiments support the Applicants' assertion that Ma does NOT enable the person of ordinary skill to make or use his synthetic route, as Ma did not obtain the claimed product at any significant level.

In the Interview, attention was then turned to the §103 rejection. Applicants made the point that the combination of the two cited documents did not enable preparation of the compounds of instant claim 113 and all other pending claims dependent thereon. Applicants asserted that Alkorta, a purely computational study wherein no actual molecules had been synthesized, disclosed some 19 different structures, that were ranked by computational processes in terms of the similarity to the peptide turn structure they were adapted to mimic, and that the 1,4-diazepane skeleton of the compounds of the instant claims was ranked well down the list. In other words, the person of ordinary skill would hardly select even the correct skeleton for the presently claimed compounds from Alkorta's ranking, as they were generally ranked as mediocre at best. And, Alkorta provides absolutely no guidance about possible synthetic preparation of the class of instantly claimed seven-membered ring compounds. The Gardner document was then discussed in terms of the structures it disclosed, none of which were seven-membered rings, but rather were nine-, eleven- and thirteen-membered rings of very different structural type from the

instantly claimed compounds. Thus, the disclosure of Gardner would not lead to the selection of the instantly claimed 1,4-diazepanes, either the skeletons or the substituents. As such, synthetic procedures disclosed by Gardner would not enable the preparation of applicants' compounds. In short, the combination of Alkorta and Gardner, coupled with the knowledge of a person of ordinary skill, did not direct one to the instantly claimed compounds or teach how to prepare any such compounds. The Examiner appeared to take this under consideration.

At this point the interview was terminated. Applicants wish to thank Examiner Grossman and the others in attendance for the substantial amount of time and attention they provided to applicants at the interview. No general agreement was reached, but the Examiner agreed to consider further information that Applicants would present in the course of examination of the application, for which Applicants herein file a Request for Continued Examination.

Applicants provide herein a copy of the original Declaration discussed at the Interview, and, and also submit herewith a new Declaration in which the experimental series discussed at the Interview was carried out.

Election/Restrictions

We note the currently pending claims are claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138, and 140. In the event that during the further prosecution of the application the elected species is found to be free of the prior art we request that the withdrawn claims be included within the search in accordance with Markush practice (**MPEP 803.02**).

Rejection under 35 USC §102

In the office action the examiner rejected claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 as being anticipated by Ma et al. (1995 Protein Peptide Letters 2: 347-350).

As previously stated and submitted at the interview with the examiner on November 13 2007 Applicants submit that while the Ma document may depict a structure within the scope of independent claim 113, this document is not enabling for the structure depicted. In particular it is Applicants' position that Ma did not in fact obtain the actual compound depicted in the document but rather had obtained an isomer that did not contain a seven membered ring. In

support of this proposition we submit a statutory declaration of Professor Ian D Jenkins, attached hereto, which we refer to hereafter as the "first Declaration".

Without wishing to repeat the contents of the first Declaration, Applicants point out that in paragraph 7, Professor Jenkins emphasizes that in his opinion the cyclization product from the Ma precursor is not the 1,4-diazepan-2-one structure(2) claimed. Professor Jenkins comes to this conclusion on the basis that 3 and 5 membered rings are much more readily formed than 7 membered rings. The relevant portion of the Jenkins declaration is as follows:

7. I have examined the paper by Xin Ma et al (*Prot. Peptide Lett.*, 1995, 347-350) and consider that the cyclisation product from the Mitsunobu reaction is certainly not the 1,4-diazepan-2-one structure (2) that they claim. Indeed I am surprised that this paper was accepted by the referee(s) as it is well known by those skilled in the art, that three and five-membered rings are far more easily formed than seven-membered rings (the rate of formation of five-membered rings is typically 10,000 times faster than for seven-membered rings – see *Advanced Organic Chemistry* by Carey and Sundberg, 3rd edition, Plenum, NY, 1990, p163). Given this fact, the referee(s) should have insisted that Ma et al provide evidence for the formation of a seven-membered ring. No such evidence was provided. The MS and microanalytical data provide evidence for the molecular formula, but not the structure. The ¹H NMR spectrum, was not assigned, and only provides evidence for a molecule with 43 protons.

As can be seen from the paragraph Professor Jenkins considers that not only is it more likely that the product disclosed in Ma is either the 3 or 5 membered ring isomer but in addition that there is no experimental evidence provided in Ma to establish, unambiguously that the seven membered ring was formed. As stated by Professor Jenkins the data, such as there was only established the molecular formula not the gross structure.

In addition in paragraph 9 of his declaration Professor Jenkins provides an analysis of the reported carbon-13 NMR data from Mimetica and concludes that in his opinion the spectral data is more consistent with the product being the Boc-Aziridine derivative and not the structure

proposed by Ma. For the examiners convenience the paragraph from the Jenkins declaration is reproduced below.

9. The ^{13}C chemical shift of the Boc carbonyl is very characteristic and where you would expect it to be (generally 161-163 ppm) for a Boc-aziridine [see S. Quader, S. E. Boyd, I. D. Jenkins, and T. A. Houston, *J. Org. Chem.*, 2007, **72**, 1962-1979; *J. Org. Chem.*, 2007, **72**, 1962; *J. Org. Chem.*, 2001, **66**, 1657; *J. Org. Chem.*, 1994, **59**, 4875; *J. Chem. Soc. Perkin 1*, 2001, 1916; *Tetrahedron* 2002, 5231; *Org. Lett.* 2001, **3**, 2349; *Synlett* 1998, 247]. I would expect the oxazoline to have a shift of about 157 ppm. Moreover, there are many examples of aziridine formation from hydroxy Boc-amines. A SciFinder substructure search gave no hits for oxazoline formation. The only literature examples of oxazoline formation are with amides (as in the paper by Galeotti et al, *Tet. Lett.*, 1992, 2807). There are no examples with N-Boc amines which are carbamates. Certainly, the ^{13}C chemical shift observed for the Boc carbonyl (160.7 ppm) is inconsistent with the structure (2) proposed by Ma et al. Such a structure would be expected to have a chemical shift for the Boc carbonyl very close to that of the starting material (1), ie, between 155 and 157 ppm.

Accordingly in sum it is Applicants' position that the structure depicted in Ma is the result of an incorrect structural assignment of the reaction product from the reaction carried out by Ma and therefore is not enabling as it does not provide a skilled worker in the art with the tools to produce the depicted 1,4-diazacycloheptane (diazepane) structure.

Nevertheless it is the understanding of the Applicants from the Interview that the Examiner was of the opinion that the experimental work carried out by the Applicants as described in the first Declaration was insufficient to displace the presumption of validity of the Ma reference. It was the applicants understanding that the concerns of the examiner included the following:

- (1) That only one set of conditions was tested in repeating the Ma reaction;
- (2) That a different route was used to prepare the Mitsunobu precursor;

(3) That the crude Mitsunobu product obtained by Dr Cassidy was not specifically analyzed to eliminate the possibility that minor amounts (down to about 1%) of the structure claimed by Ma were produced.

In raising the objection of anticipation of the present claims in light of Ma the examiner also states in the office action that:

Ma et al also present in scheme 1 as an alternative pathway for preparing said 1,4 diazacycloheptane derivatives which *does not employ* Mitsunobo chemistry (see also pg 348 first line "Two strategies have been studied"), however applicant has not presented data to refute this pathway in said declaration or elsewhere in the application. Thus, Applicants' arguments and evidence are not commensurate in scope with the teachings of Ma.

With respect to the examiner it is submitted that all that is disclosed in scheme 1 of the Ma document is the synthesis of a cyclisation precursor (6). There is no teaching or suggestion that this precursor was ever subjected to cyclisation conditions, or what further reactions and cyclization conditions would be required and thus it is submitted that this does not provide any enablement for the compounds of formula (1) of Ma. Indeed in the document Ma make clear that "*we have no longer pursued beyond the step of protected α,β -ketodiamine 6*". As such it is submitted that as this first scheme does not provide a pathway to the compounds of formula 1 but merely provides the synthesis of a possible cyclisation precursor there is no need on the part of the applicant to provide data to refute this pathway. There is no evidence in Ma that this cyclisation precursor can be used to produce a 7 membered cyclisation product.

The Applicants accordingly have carried out a more extensive series of experiments, as was agreed in the Examiner's Interview, addressing these perceived deficiencies. The present accompanying Declaration (referred to hereinafter as the "second Declaration") provides a systematic exploration of the reaction conditions that were discussed at the Interview as those a

person of ordinary skill would vary in order to determine whether any variations of the reaction conditions that would be considered by a skilled artisan would lead to any formation of the 7 membered ring compound cyclization product that Ma claims to have prepared.

The protocol includes experiments in which there are variations in the following:

- (1) order of addition of reagents;
- (2) reaction time;
- (3) reaction temperature; and
- (4) reaction solvent.

Summarizing the results that are presented in detail in the second Declaration, none of the seven-membered ring compound that Ma claimed to have prepared was detected as being formed under any of the sets of conditions examined.

Since none of the range of tested conditions outlined in the second Declaration resulted in the formation of any detectable amount of the seven-membered ring compound, it is submitted that the Ma document is not enabling for the production of the seven membered compounds of the present invention.

This being the case, Ma cannot anticipate the instantly pending claims. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 USC §103

In the office action the Examiner rejected the instant claims as being unpatentable over Gardner (Tetrahedron 49:3433-3448) in view of Alkorta (1996 J. Molecular Modeling 2:16-25).

Applicants submit that the synthesis of the seven-membered ring compounds of the present invention is not enabled in any way by either of these documents (nor is it enabled by the Ma reference as detailed above; nor is it within ordinary skill, Applicants submit).

In addition it is submitted that a skilled artisan would not be led to the present invention from the combination of references as detailed by the Examiner. In particular neither Gardner nor Alkorta nor the combination teach any way to make the compounds of the invention, and thus in the absence of an independent enabling synthesis, Gardner and Alkorta are not enabling either by themselves or in combination. Alkorta disclose 19 different skeleton structures and makes clear that the 1,4-diazepane structure is not at the top of the list of good matches for the hydrogen bonded target structure (i.e the peptide turn structure being mimicked). Therefore, it is submitted that a skilled artisan upon reading Alkorta would not be motivated to use the 1,4-diazepane structure, as a person of ordinary skill in the art would not select a mediocre match when better matches were available. In addition, the Alkorta reference is wholly silent with respect to the substitution pattern on the ring skeletons, and certainly does not disclose any of the substituents of the seven-membered ring compound of present claim 113.

In relation to the combination of Gardner with Alkorta, it is respectfully submitted that the Gardner reference does not overcome the shortcomings of the Alkorta reference as discussed above, nor does it provide any enablement for the production of the compounds of the invention. Gardner does not provide any guidance whatsoever in relation to the construction of seven-membered ring compounds of this class, being directed solely to the construction of 9-, 11- and 13- membered rings of substantially different structure. In addition, as pointed out to the Examiner at the Interview, Dr. Blaskovich worked with the Gardner group and he was of the opinion that the chemistry detailed in Gardner was not applicable to the formation of seven membered ring compounds. Thus, it is submitted that a skilled artisan in the field would not consider that Alkorta and Gardner could be combined, and even if they did, they would not arrive at the compounds of the present invention as they would not select the claimed structure from among many possible alternatives, given the fact that it is depicted as being a mediocre match for the intended target in comparison to other structures.

CONCLUSION

In response to the Notice of Non-Compliant Amendment and in accordance with 37 CFR §1.121, Applicants have corrected and resubmitted the entire Response for the Examiner's consideration. Applicants further attach a new Declaration (second Declaration) by the inventors herein addressing the perceived deficiencies of the first Declaration, also accompanying this Response.

Applicant respectfully submits that the Examiner withdraw the non-compliant status and examine the Response as appropriate.

The Examiner is invited to telephone Applicants' attorney at (612) 373-6941 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6941

Date Sept 23, 2008

By Geoffrey K. Cooper
Geoffrey K. Cooper
Reg. No. 51,266

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 23rd day of September 2008.

CHERYL L. DANKERS

Name

Cheryl Dankers
Signature

EXPEDITED PROCEDURE – EXAMINING GROUP 1639

S/N 09/647,054

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Peter Joseph Cassidy et al.

Examiner: Christopher M.

Gross

Serial No.: 09/647,054

Group Art Unit: 1639

Filed: February 6, 2001

Docket No.: 707.025US1

Title: PEPTIDE TURN MIMETICS

AMENDMENT & RESPONSE UNDER 37 C.F.R. 1.116 and
DECLARATION UNDER 37 C.F.R. 1.132

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In response to the Final Office Action mailed July 25, 2007, please amend the application as follows:

This response is accompanied by a Petition, as well as the appropriate fee, to obtain a three-month extension of the period for responding to the Office action, thereby moving the deadline for response from October 25, 2007 to January 25, 2008.

A declaration submitted under 37 C.F.R. §1.132 is submitted herewith.

A summary of the personal Examiner interview of Nov. 13, 2007, in this matter is provided herein.

IN THE CLAIMS

Pending claims are as follows, no amendments are made.

1-112. (Canceled)

113. (Previously Presented) A general mimetic of the structure

wherein:

indicates a bond at a chiral centre of the structure which centre may be in the R or S configuration or a mixture thereof;

R, R¹ and R² are amino acid side chain groups which may be the same or different;

M' and M'' may be the same or different and are selected from the group consisting of hydrogen, C₁-C₄ alkyl, chloro and C₁-C₄ alkoxy;

M³, M⁴, M⁵ and M⁶ define a lactam as follows:

(i) M³, M⁴ when taken together with the ring carbon to which they are attached form a carbonyl group, M⁵ and M⁶ = H, or

(ii) M³ is H and M⁴ = M', M⁵ and M⁶ when taken together with the carbon atom to which they are attached form a carbonyl group;

Z' is selected from the group consisting of hydrogen or methyl or part of a cyclic amino acid sidechain joined to R¹;

Pg^N is a protecting group for amine;

R^C is selected from the group consisting of a carboxy terminal part of the mimetic, hydrogen, R, and CH_2R ; and

Z is selected from the group consisting of hydrogen, methyl, ethyl, formyl, acetyl, $-CH_2R$, and $C(O)R$.

114. (Withdrawn) A peptide mimetic as claimed in claim 113 wherein when Q^1 and Q^2 form a cyclic group Q^1Q^2 which is selected from the group consisting of $-CH(R)C(O)-$, $-CH_2CH(R)C(O)-$, $-CH_2CH_2CH(R)C(O)-$, $-CH(R)CH_2-$, $-CH_2CH(R)CH_2-$, $-CH_2CH_2CH(R)CH_2-$, $-CH_2CH(R)-$, $-CH_2CH_2CH(R)-$, $-CH(R)CH_2CH_2-$, $-CH_2CH(R)CH_2CH_2-$, $-CH(R)CH_2C(O)-$ and $-CH_2CH(R)CH_2C(O)-$.

115. (Withdrawn) A peptide mimetic as claimed in Claim 113 wherein Q^1 is R, Q^2 is Z, Q^3 is $C(O)$ or CH_2 .

116. (Withdrawn) A peptide mimetic as claimed in Claim 113 wherein Q^1 is R, Q^2 is Z, Q^3 is $-C(O)N(Q^5)CH(R)C(O)-$ or $-C(O)N(Q^5)CH(R)CH_2-$.

117. (Withdrawn) A peptide mimetic as claimed in Claim 113 wherein Q^1 is $CH(R)C(O)Q^2$, Q^1Q^2 – forms a cyclic group $-CH(R)C(O)-Q^2$, Q^3 is $C(O)$ or CH_2 .

118. (Withdrawn) A peptide mimetic as claimed in Claim 113 wherein Q^1 is $CH_2CH(R)C(O)Q^2$, Q^1Q^2 – forms a cyclic group $-CH_2CH(R)C(O)-$, Q^3 is $C(O)$ or CH_2 .

119. (Previously Presented) A peptide mimetic as claimed in Claim 113 wherein R^C is $C(O)Pg^C$ where Pg^C is a protecting group for carboxylic acid.
120. (Previously Presented) A peptide mimetic as claimed in Claim 119 wherein Pg^C is selected from the group consisting of alkoxy, benzyloxy, allyloxy, fluorenylmethyloxy, amines forming easily removable amides, a cleavable linker to a solid support, the solid support, hydroxy, NHR, OR, R or the remaining C-terminal portion of the mimetic.
121. (Previously Presented) A peptide mimetic as claimed in Claim 113 wherein Pg^N is selected from a group consisting of Boc, Cbz, Alloc, trityl, a cleavable linker to a solid support, the solid support, hydrogen, R, $C(O)R$ or part of the remaining N-terminal portion of the mimetic.
122. (Withdrawn) A peptide mimetic as claimed in Claim 113 wherein M' or M'' is methoxy.
123. (Withdrawn) A peptide mimetic is claimed in Claim 113 wherein M' or M'' is methyl.
124. (Previously Presented) A peptide mimetic as claimed in Claim 113 wherein Z is H, Z^1 is H and R^C is $C(O)Pg^C$.
125. (Withdrawn) A peptide mimetic as claimed in Claim 124 wherein R^1 and $R^2 \neq H$
126. (Previously Presented) A peptide mimetic as claimed in claim 113 wherein Z is hydrogen, M^5 and M^6 when taken together with the carbon atom to which they are attached form a carbonyl group, $Z^1 = H$, and R^C is $C(O)Pg^C$.
127. (Withdrawn) A peptide mimetic as claimed in Claim 126 wherein R^1 and $R^2 \neq H$

128. (Withdrawn) A peptide mimetic as claimed in Claim 113 wherein Q^1 is R^1 , Q^2 is hydrogen, Q^3 is $-C(O)N(Q^5)CH(R)C(O)-$, $Z^1=H$ and R^C is $C(O)Pg^C$.

129. (Withdrawn) A peptide mimetic as claimed in Claim 113 wherein Q^1 is R^1 , Q^2 is hydrogen, Q^3 is $-C(O)N(Q^5)CH(R)CH_2-$, $Z^1=H$ and R^C is $C(O)Pg^C$.

130. (Withdrawn) A peptide mimetic as claimed in Claim 114 wherein Q^1Q^2 is $-CH(R^2)C(O)-$, Q^3 is $C(O)$, $Z^1=R^1$ and R^C is $C(O)Pg^C$.

131. (Withdrawn) A peptide mimetic as claimed in Claim 114 wherein Q^1Q^2 is $-CH(R^2)C(O)-$, Q^3 is CH_2 , $Z^1=R^1$ and R^C is $C(O)Pg^C$.

132. (Withdrawn) A peptide mimetic as claimed in Claim 114 wherein Q^1Q^2 is $-CH_2CH(R^2)C(O)-$, Q^3 is $C(O)$, $Z^1=R^1$ and R^C is $C(O)Pg^C$.

133. (Withdrawn) A peptide mimetic as claimed in Claim 114 wherein Q^1Q^2 is $-CH_2CH(R^2)C(O)-$, Q^3 is CH_2 , $Z^1=R^1$ and R^C is $C(O)Pg^C$.

134. (Previously Presented) A peptide mimetic according to claim 113 wherein R , R^1 and R^2 are each independently selected from the group consisting of

- (i) $-CH_3$,
- (ii) ,
- (iii) $-CH_2SH$,
- (iv) $-CH_2CH_2-C(O)NH_2$,
- (v) $-H$,
- (vi) $-CH(CH_3)CH_2CH_3$,
- (vii) $-CH_2-CH(CH_3)_2$,
- (viii) $-CH_2CH_2S-CH_3$,

- (ix) -CH₂Ph,
- (x) -CH₂OH,
- (xi) -CH(OH)CH₃,
- (xii) -CH₂-(3-indolyl)
- (xiii) -CH₂-Ph-OH,
- (xiv) -CH(CH₃)₂,
- (xv) -CH₂CO₂H,
- (xvi)
- (xvii)
- (xix) -CH₂-CH₂-CH₂-CH₂-NH₂.
- (xx) -CH₂CH₂CO₂H.

135. (Previously Presented) A mimetic according to claim 113 having the structure:

136. (Withdrawn) A mimetic according to claim 113 having the structure:

137. (Previously Presented) A peptide mimetic as claimed in claim 135 wherein M', M'' are H.

138. (Previously Presented) A peptide mimetic as claimed in claim 135 wherein Z, Z¹ are H.

139. (Withdrawn) A peptide mimetic as claimed in claim 135 wherein R¹ and R² ÿ H.

140. (Previously Presented) A peptide mimetic as claimed in claim 135 wherein R^C is C(O)Pg^C where Pg^C is a protecting group for carboxylic acid.

141. (Withdrawn) A peptide mimetic as claimed in claim 136 wherein M', M'' are H.
142. (Withdrawn) A peptide mimetic as claimed in claim 136 wherein Z, Z¹ are H.
143. (Withdrawn) A peptide mimetic as claimed in claim 136 wherein R¹ and R² ÿ H.
144. (Withdrawn) A peptide mimetic as claimed in claim 136 wherein R^C is C(O)Pg^C where Pg^C is a protecting group for carboxylic acid.

REMARKS

This responds to the Office Action mailed on July 25, 2007.

No claims are amended, no claims are canceled, and no claims are added; as a result, claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 are now pending in this application.

Interview Summary

A personal applicant-initiated Examiner Interview in the above-referenced matter, concerning the Final Office Action dated 07/25/2007, took place at the U.S. Patent Office on Nov. 13, 2007. In attendance were Examiners Christopher M. Gross, Mark Shibuya, and Jon Epperson, and applicants' representative Mark Blaskovich of Mimetica Ltd. (patent licensee) and patent attorneys Gary Speier and Geoffrey Cooper, representing the applicants.

All presently pending claims not withdrawn, i.e., claims 113, 119-121, 124, 126, 134, 135, 137, 138, and 140 were discussed in view of the claim rejections under 35 USC §102(b) over Ma, and under 35 USC §103 over Gardner in view of Alkorta. The instant pending claims are directed to seven-membered ring structures designed to mimic a particular type of turn in a peptide chain, thus mimicking a domain of a protein made up of a folded peptide chain incorporating this kind of turn. The seven-membered ring structures of the pending claims, termed 1,4-diazepanes, must effectively mimic this turn structure in order to have the desired bioactivity as a medicinal compound. Structures involving other ring sizes are not within the scope of the pending claims.

Concerning the §102 rejection, an exhibit, a declaration by the inventor herein, Dr. Cassidy, was provided to the Examiners, pertinent to the applicants' assertion that the Ma reference cannot be used as the basis for a §102 rejection because Ma is not enabling to a person of ordinary skill. The declaration presented evidence in support of the applicants' assertion that Ma had actually prepared an isomer of the structure shown in the Ma reference, not the seven-membered ring product shown therein that Ma believed he had obtained. The structure shown by Ma had been used by the Examiner as the basis for the §102 rejection. The report described

results of experiments that had been carried out, duplicating Ma's experimental procedures, and providing spectroscopic data in support of the assertion that Ma's product was not in fact a seven-membered ring such as are claimed in the instant application, but was an isomeric three- or five-membered ring structure that was misidentified by Ma.

Arguments were then presented to the Examiners in attendance. With respect to the §102 rejection, applicants first addressed the Examiner's assertion that Ma disclosed two separate routes to his alleged seven-membered ring product. It is applicants' position that Ma only disclosed two separate possible routes to the single precursor compound for the cyclization reaction alleged to produce the seven-membered ring, not to the seven-membered ring itself. The Examiner apparently found this argument unpersuasive, but could not direct applicants' attention to any language in support of there being a second route used in the direct preparation of the seven-membered ring product. The sole process applicants believe to be disclosed by Ma, alleged to yield the seven-membered ring product, a Mitsunobu reaction, was duplicated as described in the declaration exhibit. It is the applicants' position that there is no second approach was disclosed by Ma to be duplicated.

Then, applicants discussed the spectroscopic evidence provided in the declaration in support of the alternative isomeric structure that Ma had in fact obtained, as opposed to the seven-membered ring structure that Ma thought he had obtained. The Examiner seemed to feel that even if the major product isolated from the reactions carried out by Dr. Cassidy and presented in the declaration was not Ma's structure, insufficient investigation had been conducted to have a high degree of certainty that the seven-membered ring compound was not also present in the reaction product in some yield, that would serve to provide enablement to the person of ordinary skill using Ma's method. The applicants also understood the Examiner to assert that Ma's disclosed structure and synthetic approach, coupled with a reasonable degree of experimentation in variation of reaction condition such as a person of ordinary skill could be expected to carry out, could in fact make Ma enabling, and thus anticipatory. Alternatively, it is believed that the Examiner took the position that Ma's structural disclosure, combined with the knowledge of a person of ordinary skill, would make the instant pending claims obvious over Ma. Applicants maintained that if the Mitsunobu cyclization reaction failed to take place in the manner disclosed by Ma, as applicants' data suggests, that it is not within ordinary skill to

prepare the difficult seven-membered ring structure without undue experimentation. Furthermore, having found that Ma's Mitsunobu conditions failed, applicants believe that a person of ordinary skill would be motivated against extensive exploration of Mitsunobu conditions, and that no generally known alternative reactions using those precursors are available.

The applicants then attempted to determine what nature and quantity of evidence would be required for the Examiner to find sufficiently persuasive to overcome the presumption of validity of the Ma reference. The Examiner indicated, as applicants understand it, that he thought a factorial series of reactions should be run, exploring to a reasonable extent (without undue experimentation) variations in reaction conditions. Furthermore, each reaction product should be carefully analyzed for trace amounts of the seven-membered ring product, down to about the 1% yield level, as the compound would have to be recoverable from the reaction for the process to be enabled and yields of less than about 1% would be impractical in that regard.

Attention was then turned to the §103 rejection. Applicants made the point that the combination of the two cited documents did not enable preparation of the compounds of instant claim 113 and all other pending claims dependent thereon. Applicants asserted that Alkorta, a purely computational study wherein no actual molecules had been synthesized, disclosed some 19 different structures, that were ranked by computational processes in terms of the similarity to the peptide turn structure they were adapted to mimic, and that the 1,4-diazepane skeleton of the compounds of the instant claims was ranked well down the list. In other words, the person of ordinary skill would hardly select even the correct skeleton for the presently claimed compounds from Alkorta's ranking, as they were generally ranked as mediocre at best. The Gardner document was then discussed in terms of the structures it disclosed, none of which were seven-membered rings, but rather were nine-, eleven- and thirteen-membered rings of very different structural type from the instantly claimed compounds. Thus, the disclosure of Gardner would not lead to the selection of the instantly claimed 1,4-diazepanes, either the skeletons or the substituents. As such, synthetic procedures disclosed by Gardner would not enable the preparation of applicants' compounds. In short, the combination of Alkorta and Gardner, coupled with the knowledge of a person of ordinary skill, did not direct one to the instantly

claimed compounds or teach how to prepare any such compounds. The Examiner appeared to take this under consideration.

At this point the interview was terminated. Applicants wish to thank Examiner Grossman and the others in attendance for the substantial amount of time and attention they provided to applicants at the interview. No general agreement was reached, but the Examiner agreed to consider further information that applicants will present in the course of examination of the application, for which applicants herein file a Request for Continued Examination.

Election/Restrictions

We note the currently pending claims are claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138, and 140. In the event that during the further prosecution of the application the elected species is found to be free of the prior art we request that the withdrawn claims be included within the search in accordance with Markush practice (MPEP 803.02).

Rejection under 35 USC 102

In the office action the examiner rejected claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 as being anticipated by Ma et al (1995 Protein Peptide Letters 2: 347-350).

As previously stated and submitted at the interview with the examiner on November 13 2007 the applicants submit that whilst the Ma document may depict a structure within the scope of independent claim 113 this document is not enabling for the structure depicted. In particular it is the applicant's position that Ma did not in fact obtain the actual compound depicted in the document but rather had obtained an isomer that did not contain a seven membered ring. In support of this proposition we submit a statutory declaration of Professor Ian D Jenkins.

Without wishing to repeat the contents of the Jenkins declaration the applicants point out that in paragraph 7 Professor Jenkins emphasises that in his opinion the cyclisation product from the Ma precursor is not the 1,4-diazapan-2-one structure(2) claimed. Professor Jenkins comes to this conclusion on the basis that 3 and 5 membered rings are much more readily formed than 7 membered rings. The relevant portion of the Jenkins declaration is as follows:

7. I have examined the paper by Xin Ma et al (*Prot. Peptide Lett.*, 1995, 347-350) and consider that the cyclisation product from the Mitsunobu reaction is certainly not the 1,4-diazepan-2-one structure (2) that they claim. Indeed I am surprised that this paper was accepted by the referee(s) as it is well known by those skilled in the art, that three and five-membered rings are far more easily formed than seven-membered rings (the rate of formation of five-membered rings is typically 10,000 times faster than for seven-membered rings – see *Advanced Organic Chemistry* by Carey and Sundberg, 3rd edition, Plenum, NY, 1990, p163). Given this fact, the referee(s) should have insisted that Ma et al provide evidence for the formation of a seven-membered ring. No such evidence was provided. The MS and microanalytical data provide evidence for the molecular formula, but not the structure. The ¹H NMR spectrum, was not assigned, and only provides evidence for a molecule with 43 protons.

As can be seen from the paragraph Professor Jenkins considers that not only is it more likely that the product disclosed in Ma is either the 3 or 5 membered ring isomer but in addition that there is no experimental evidence provided in Ma to establish, unambiguously that the seven membered ring was formed. As stated by Professor Jenkins the data, such as there was only established the molecular formula not the gross structure.

In addition in paragraph 9 of his declaration Professor Jenkins provides an analysis of the reported carbon-13 NMR data from Mimetica and concludes that in his opinion the spectral data is more consistent with the product being the Boc-Aziridine derivative and not the structure proposed by Ma. For the examiners convenience the paragraph from the Jenkins declaration is reproduced below.

9. The ^{13}C chemical shift of the Boc carbonyl is very characteristic and where you would expect it to be (generally 161-163 ppm) for a Boc-aziridine [see S. Quader, S. E. Boyd, I. D. Jenkins, and T. A. Houston, *J. Org. Chem.*, 2007, **72**, 1962-1979; *J. Org. Chem.*, 2007, **72**, 1962; *J. Org. Chem.*, 2001, **66**, 1657; *J. Org. Chem.*, 1994, **59**, 4875; *J. Chem. Soc. Perkin 1*, 2001, 1916; *Tetrahedron* 2002, 5231; *Org. Lett.* 2001, **3**, 2349; *Synlett* 1998, 247]. I would expect the oxazoline to have a shift of about 157 ppm. Moreover, there are many examples of aziridine formation from hydroxy Boc-amines. A SciFinder substructure search gave no hits for oxazoline formation. The only literature examples of oxazoline formation are with amides (as in the paper by Galeotti et al, *Tet. Lett.*, 1992, 2807). There are no examples with N-Boc amines which are carbamates. Certainly, the ^{13}C chemical shift observed for the Boc carbonyl (160.7 ppm) is inconsistent with the structure (2) proposed by Ma et al. Such a structure would be expected to have a chemical shift for the Boc carbonyl very close to that of the starting material (1), ie, between 155 and 157 ppm.

Accordingly in sum it is the applicant's position that the structure depicted in Ma is the result of an incorrect structural assignment of the reaction product from the reaction carried out by Ma and therefore is not enabling as it does not provide a skilled worker in the art with the tools to produce the depicted 1,4-diazacycloheptane (diazepane) structure.

As previously submitted the present applicants attempted to repeat the cyclisation allegedly disclosed in Ma with no success as detailed in pages 66 to 72 of the present application and as explained in the declaration of Dr Peter Joseph Cassidy previously on file. All attempts by the present applicants to repeat the cyclisation reported by Ma have been unsuccessful to date (producing instead an isomer of the target derivative not having a seven membered ring, as demonstrated by NMR and chemical transformation).

Nevertheless it is the understanding of the applicants that the examiner is of the opinion that the experimental work carried out by the applicants to date is insufficient to displace the

presumption of validity of the Ma reference. It is the applicants understanding that the concerns of the examiner included the following:

- (1) That only one set of conditions was tested in repeating the Ma reaction;
- (2) That a different route was used to prepare the Mitsunobu precursor;
- (3) That the crude Mitsunobu product obtained by Dr Cassidy was not specifically analysed to eliminate the possibility that minor amounts of the structure claimed by Ma were produced.

The applicants are presently in the process of conducting a series of experiments in order to address the concerns raised by the examiner. In particular the experimental protocol being developed will involve synthesis of the Ma cyclisation precursor by the same route as detailed in scheme 2 in Ma in order to remove any possibility that the synthesis of the precursor may have an effect on the reaction of the compound. In addition the protocol will attempt the synthesis of genuine product (1) as depicted in Ma via a different synthetic route so that this material may be used as a HPLC standard by which to test the reaction mixtures obtained by the various experiments in order to demonstrate unambiguously whether the reaction mixtures contain even minor amounts of the alleged Ma cyclisation product.

In addition the experimental protocols will attempt to provide a systematic exploration of the reaction conditions that may be varied in order to determine whether any variations of the reaction conditions that would be considered by a skilled addressee would lead to any formation of the 7 membered cyclisation product allegedly formed by Ma. The protocol will include experiments in which there are variations in the following:

- (1) order of addition of reagents;
- (2) reaction time;
- (3) reaction temperature; and
- (4) reaction solvent.

As the examiner will appreciate it will take some time to conduct a comprehensive set of experiments as detailed above and the examiner is requested to delay issuing a further office action until the applicants have been able to collate the results and submit them in declaratory form.

In raising the objection of anticipation of the present claims in light of Ma the examiner also states in the office action that:

Ma et al also present in scheme 1 as an alternative pathway for preparing said 1,4 diazacycloheptane derivatives which *does not employ Mitsunobo chemistry* (see also pg 348 first line "Two strategies have been studied"), however applicant has not presented data to refute this pathway in said declaration or elsewhere in the application. Thus, Applicants' arguments and evidence are not commensurate in scope with the teachings of Ma.

With respect to the examiner it is submitted that all that is disclosed in scheme 1 of the Ma document is the synthesis of a cyclisation precursor (6). There is no teaching or suggestion that this precursor was ever subjected to cyclisation conditions, or what further reactions and cyclization conditions would be required and thus it is submitted that this does not provide any enablement for the compounds of formula (1) of Ma. Indeed in the document Ma make clear that "*we have no longer pursued beyond the step of protected α,β -ketodiamine 6*". As such it is submitted that as this first scheme does not provide a pathway to the compounds of formula 1 but merely provides the synthesis of a possible cyclisation precursor there is no need on the part of the applicant to provide data to refute this pathway. There is no evidence in Ma that this cyclisation precursor can be used to produce a 7 membered cyclisation product.

In conclusion it is submitted that the Ma document is not enabling for the production of the seven membered compounds of the present invention. The applicants submit that the declarations of both Dr Cassidy and Professor Jenkins establish that the structural assignment in Ma is

incorrect. As stated above the applicants are in the process of conducting a series of controlled experiments in which a number of variables in the Ma cyclisation are varied in order to determine whether there are any reaction conditions under which even minor amounts of the alleged Ma cyclisation precursor are made. The results of these experiments will be forwarded to the examiner as soon as they are available.

Rejection under 35 USC 103

In the office action the examiner rejected the claims as being unpatentable over Gardner (Tetrahedron 49:3433-3448) in view of Alkorta (1996 J. Molecular Modeling 2:16-25).

The applicants submit that the synthesis of the 7 membered compounds of the present invention is not enabled in any way by either of these documents (nor is it enabled by the Ma reference as detailed above).

In addition it is submitted that a skilled addressee would not be lead to the present invention from the combination of references as detailed by the examiner. In particular neither Gardner nor Alkorta nor the combination teach any way to make the compounds of the invention and thus in the absence of an independent enabling synthesis Gardner and Alkorta are not enabling. Further, Alkorta disclose 19 different skeleton structures and makes clear that the 1,4-diazepane structure is not at the top of the list of good matches for the hydrogen bonded target structure (i.e the situation being mimicked). As such upon reading the prior art it is submitted that a skilled addressee upon reading Alkorta would not be motivated to use the 1,4-diazepane structure as a person skilled in the art would not select a mediocre match when better matches were available. In addition the Alkorta reference is wholly silent with respect to the substitution pattern on the ring skeletons and certainly does not disclose any of the substituents of the ring of present claim 113.

In relation to the combination of Gardner with Alkorta it is respectively submitted that the Gardner reference does not overcome the shortcomings of the Alkorta reference as discussed above nor does it provide any enablement for the production of the compounds of the invention.

Gardner does not provide any guidance whatsoever in relation to the construction of seven membered ring systems of this class being directed solely to the construction of 9-, 11- and 13-membered rings of substantially different ring construction. In addition as pointed out to the examiner at the interview Dr Blaskovich worked with the Gardner group and he was of the opinion that the chemistry detailed in Gardner was not applicable to the formation of seven membered rings. As such it is submitted that a skilled addressee in the field would not consider that Alkorta and Gardner could be combined and even if they did they would not arrive at the compounds of the present invention as they would not select the claimed structure (from among many possible alternatives) given the fact that it is depicted as being a mediocre match for the intended target in comparison to other structures.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612) 359-3261 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 359-3261

Date: January 21, 2008

By Geoffrey K. Cooper
Geoffrey K. Cooper
Reg. No: 51,266

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 21st day of January 2008.

PATRICIA A. HULTMAN

Name

Patricia A. Hultman

Signature

DECLARATION UNDER 37 CFR § 1.132
Serial Number: 09/647,054
Filing Date: Mar. 24, 1998
Title: PEPTIDE TURN MIMETICS

Page 1
Dkt: 707.025US1

S/N 09/647,054

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Peter Joseph Cassidy, et al.	Examiner:	Christopher M. Gross
Serial No.:	09/647,054	Group Art Unit:	1639
Filed:	March 24, 1998	Docket No.:	707.025US1
Title:	PEPTIDE TURN MIMETICS		

DECLARATION UNDER 37 C.F.R. §1.132

I, Ian D Jenkins, declare and say as follows:

1. I, Ian D Jenkins, received my Bachelor Degree with honours at the University of New South Wales, Sydney, Australia in 1966 and Doctorate from the University of New South Wales in 1969. I am currently a Professor of Chemistry at Griffith University which is located in Brisbane, Australia and am also the Deputy Director of Natural Product Discovery at the Eskitis Institute for Cell and Molecular Therapies located at the university. I have authored or co-authored 140 scientific publications, and am a named co-inventor on 2 patent applications.

2. I have conducted and supervised research in the area of chemical synthesis for the last 32 years with particular research interests being in the areas of the synthesis of biologically active molecules based on natural product scaffolds, medicinal chemistry, carbohydrate chemistry, organophosphorus chemistry (in particular the Mitsunobu reaction), polymer chemistry and reaction mechanisms.

3. I have been asked by Dr Peter Cassidy, to review a paper by Xin Ma et al (Prot. Peptide Lett., 1995, 347-350) and to provide my opinion on whether I consider that the cyclisation product from the Mitsunobu reaction as described in this paper is correct.

4. I have been paid by Mimetica a consultancy fee for my time in reviewing the paper and preparing this declaration.

5. I understand that during prosecution of the above patent application in the US the Examiner has rejected claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138, and 140 on the basis of 35 U.S.C. §102(b) as being anticipated by Ma et al., 1995, Protein Peptide Letters, 2:347-350.

6. I attach in the appendix the structure of the Ma cyclisation precursor (compound 1 in the appendix), as well as structures of the Ma proposed cyclisation product (compound 2 in the appendix) as well as what I understand are the two cyclisation products thought to be the most likely by Dr Cassidy to be formed (structures 3 and 4 in the appendix).

7. I have examined the paper by Xin Ma et al (*Prot. Peptide Lett.*, 1995, 347-350) and consider that the cyclisation product from the Mitsunobu reaction is certainly not the 1,4-diazepan-2-one structure (2) that they claim. Indeed I am surprised that this paper was accepted by the referee(s) as it is well known by those skilled in the art, that three and five-membered rings are far more easily formed than seven-membered rings (the rate of formation of five-membered rings is typically 10,000 times faster than for seven-membered rings – see *Advanced Organic Chemistry* by Carey and Sundberg, 3rd edition, Plenum, NY, 1990, p163). Given this fact, the referee(s) should have insisted that Ma et al provide evidence for the formation of a seven-membered ring. No such evidence was provided. The MS and microanalytical data provide evidence for the molecular formula, but not the structure. The ¹H NMR spectrum, was not assigned, and only provides evidence for a molecule with 43 protons.

8. Of the two possible structures that are proposed by Dr Cassidy, I am fairly certain that it is the N-Boc aziridine (4) that is formed, rather than the oxazoline (3) (see Scheme attached).

9. The ^{13}C chemical shift of the Boc carbonyl is very characteristic and where you would expect it to be (generally 161-163 ppm) for a Boc-aziridine [see S. Quader, S. E. Boyd, I. D. Jenkins, and T. A. Houston, *J. Org. Chem.*, 2007, **72**, 1962-1979; *J. Org. Chem.*, 2007, **72**, 1962; *J. Org. Chem.*, 2001, **66**, 1657; *J. Org. Chem.*, 1994, **59**, 4875; *J. Chem. Soc. Perkin I*, 2001, 1916; *Tetrahedron* 2002, 5231; *Org. Lett.* 2001, **3**, 2349; *Synlett* 1998, 247]. I would expect the oxazoline to have a shift of about 157 ppm. Moreover, there are many examples of aziridine formation from hydroxy Boc-amines. A SciFinder substructure search gave no hits for oxazoline formation. The only literature examples of oxazoline formation are with amides (as in the paper by Galeotti et al, *Tet. Lett.*, 1992, 2807). There are no examples with N-Boc amines which are carbamates. Certainly, the ^{13}C chemical shift observed for the Boc carbonyl (160.7 ppm) is inconsistent with the structure (2) proposed by Ma et al. Such a structure would be expected to have a chemical shift for the Boc carbonyl very close to that of the starting material (1), ie, between 155 and 157 ppm.

10. I have also reviewed the hydrolysis experiments conducted on the cyclisation product by Dr Peter Cassidy as discussed in PCT application WO99/48913 on page 69. I understand that this PCT application corresponds to the US patent application the subject of this declaration.

11. In terms of the hydrolysis experiment (mild acid hydrolysis of the cyclised product with 0.1% aq. TFA at room temperature for 12 h to give back the starting material 1), I consider that these conditions would not result in hydrolysis of the lactam 2 (Ma proposed structure) but would be consistent with an oxazoline 3. However, this result is also consistent with an N-Boc aziridine 4. In our experience, these have similar reactivities to epoxides (there is an example in our 2007 JOC paper where propylamine reacts selectively at room temperature with an N-Boc aziridine, but NaN_3 reacts with both the epoxide and the aziridine), and would be readily opened by mild acids.

12. Finally, I think that the Nouvet cyclisation (*Tetrahedron*, 1999, 4685) is another example of aziridine formation, but in this case, the aziridine undergoes subsequent ring-opening by the tosylamide anion to give the observed lactam. This is consistent with Nouvet's finding that the (acidic) sulfonamide group was essential for the cyclisation.

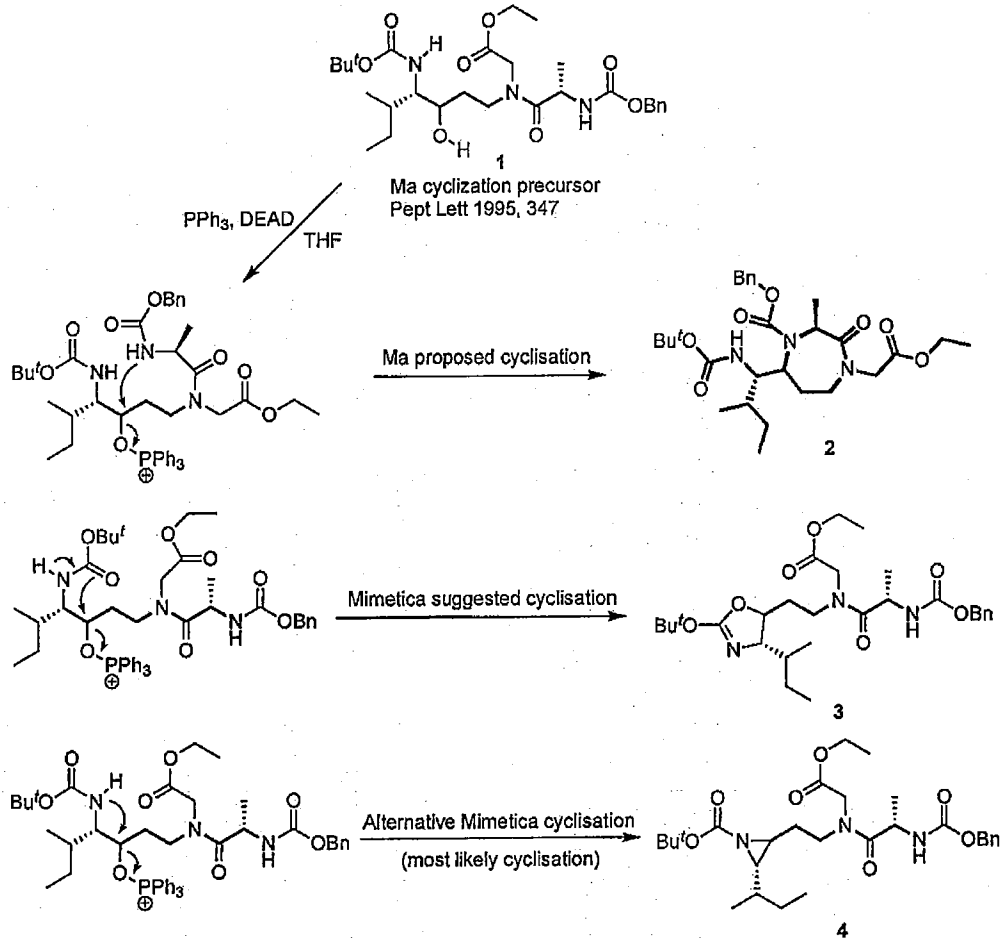
13. In conclusion, it is my opinion that treatment of the Ma cyclisation precursor 1 with triphenylphosphine and diethyl azodicarboxylate (Mitsunobu reaction) would give the aziridine 4, not the 1,4-diazepan-2-one structure 2 as claimed by Ma et al in *Prot. Peptide Lett.* 1995, 347-350.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that such willful false statement may jeopardize the validity of this application or any patent issuing therefrom.

Nov 8, 2007
Date

I. D. Jenkins
Ian D Jenkins

APPENDIX



Scheme